NIH Guidelines and Research with 1918 H1N1

December 2, 2008

Overview

- **RAC Review of Biosafety Containment and Practices for 1918 H1N1**
- **Oseltamivir Prophylaxis and 1918 H1N1**
  - **Whether to use ongoing prophylaxis for fully reconstructed 1918 H1N1 and/or recombinant influenza viruses containing genes from 1918 H1N1 is an open question that will be informed by today's proceedings**
  - **No policy has yet been recommended to NIH by the RAC**
  - **The question is how do we best balance obligations to the public health and investigators while not unnecessarily impeding important research**

NIH Guidelines: Influenza Viruses

- **Currently, all influenza viruses are classified as Risk Group (RG) 2 agents**
  - **No distinction between pandemic strains such as 1918 H1N1 and potentially less dangerous influenza viruses.**
- **While RG is not determinative of containment level and practices, it is the starting point for the risk assessment**
- ***NIH Guidelines* have not been updated since the on-line publication of the BMBL in 2007, which recommends Biosafety Level 3 (enhanced) containment for work with 1918 Influenza**

Risk Groups Under the *NIH Guidelines*

- **Risk Groups**

RG1	**Agents are not associated with disease in healthy adult humans.**
RG2	**Agents are associated with human disease which is rarely serious and for which preventive or therapeutic interventions are *often* available.**
RG3	**Agents are associated with serious or lethal human disease for which preventive or therapeutic interventions *may be* available (high individual risk and low community risk).**
RG4	**Agents are likely to cause serious or lethal human disease for which preventive or therapeutic interventions *are not usually* available (high individual risk and high community risk).**

- **Containment levels (BL, BSL)**
  - **Containment level may be raised or lowered depending on a comprehensive risk assessment.**

Approach of RAC Biosafety WG

- **Reviewed extant biosafety guidances and policies for research with 1918 pandemic influenza virus**
  - ***NIH Guidelines***
  - **CDC/NIH BMBL**
  - **CDC Influenza Division policy**
  - **Current data and literature**
- **Considered if any changes are needed to update the *NIH Guidelines* for work with 1918 H1N1**

RAC Biosafety Working Group

- June 24th Conference on Human H2N2, 1918 Influenza Virus and HPAI H5N1
- Consultation with outside experts
- Proposed Changes Presented at September 2008 RAC meeting

Risk Group Considerations for 1918 H1N1

Individual Risk

- Known to cause serious or lethal disease
- Animal data supports antivirals for prophylactic use
  - No treatment data in animals
- Possible partial immunoprotection from previous exposure to or vaccination against circulating H1N1 strains, but data is not definitive

Risk Group Considerations for 1918 H1N1

Community Risk

- Known to cause serious or lethal disease
- Animal data supports antivirals for prophylactic use
- Distribution of antivirals to general public if virus spread as rapidly as did historically
  - However, majority of 1918 deaths appear due to secondary pneumonias for which antibiotics are now available
    - ?s about impact of resistance to antibiotics
    - ?s about demands on health care system
- Partial immunoprotection possible but same caveats as for individual risk

Data that could Further Inform Biosafety Containment and Policies

- **Additional animal studies on use of antivirals against 1918 H1N1**
  - **Larger animal models**
  - **Treatment data**
- **Analysis of whether current antibodies in the general population to circulating strains of H1N1 confer protection against 1918 H1N1**

Proposed Biosafety Containment and Practices

- 1918 H1N1 is a Risk Group 3 agent
- Agreement that BMBL containment recommendations for fully reconstructed 1918 H1N1 would be appropriate for the full virus and a starting point for containment for recombinant influenza viruses containing genes from 1918 H1N1
  - Criteria needed to be developed as to when to lower containment
    - Lack of consensus on the data needed
    - Lack of consensus on most appropriate animal models
- For recombinant work with genes from 1918 H1N1 in the background of cold-adapted influenza strain the biosafety level may be lowered provided manipulation does not alter attenuation of the backbone

Occupational Health and Medical Surveillance

- **Preliminary recommendation that CDC's occupational health policies for work with the fully reconstructed 1918 virus be adopted including**
  - **Seasonal vaccine as a prerequisite**
  - **Use of antiviral prophylaxis during work**
- **Policy for recombinant work with respect to antivirals not finalized**

Ongoing Prophylaxis

Given pandemic potential, priority given to preventing any active infection in the community

Data from animal models supports antiviral prophylaxis for 1918 H1N1

- Lacking data on treatment efficacy

Post-exposure Prophylaxis

Can this be achieved with post-exposure prophylaxis?

- What is the risk of an unrecognized breach in containment?

Prophylaxis effective up to 48 hours after exposure

Reasonable to believe that mouse data on prophylaxis indicative treatment efficacy

Ongoing Prophylaxis	Post-exposure Prophylaxis
Safety of oseltamivir studied for 6 weeks in healthy volunteers and in elderly and immunocompromised ▪ **Recent 12 week study**	**What would be the safety of longer term exposure to the investigator?** **Do the potential benefits outweigh the risks?**
CDC researchers have successfully used this policy for several years	**Applies to a limited number of government researchers.** ▪ What are the safety, legal and ethical questions raised by extending this policy generally to all researchers?

Additional Considerations . . .

- What is the risk that this practice would foster resistance to oseltamivir in circulating influenza strains, 1918 H1N1?
- Should one distinguish between high risk experiments, for example animal work and other work?
- If prophylaxis is only safe for a period of time should researchers be asked to structure their experiments around these limitations?
- Should this policy only be considered for work with fully reconstructed 1918 H1N1 and why?

Questions for Consideration?

For the Fully reconstructed 1918 Influenza only?

Post-Exposure Prophylaxis Only

For Influenza Recombinants?

Ongoing Prophylaxis

For all experiments?

For high risk experiments, e.g animal work?